

CLAIMS

What Is Claimed Is:

- 5        1.    A crystalline form of a polypeptide corresponding  
to the catalytic domain of a non-insulin receptor tyrosine  
kinase.
2.    The crystalline polypeptide of Claim 1 in which the  
10 non-insulin receptor tyrosine kinase is a receptor tyrosine  
kinase.
3.    The crystalline polypeptide of Claim 1 in which the  
non-insulin receptor tyrosine kinase is a cytoplasmic  
15 tyrosine kinase.
4.    The crystalline polypeptide of Claim 2 in which the  
non-insulin receptor tyrosine kinase is FGF-R, PDGF-R, KDR,  
CCK4, MET, TRKA, AXL, TIE, EPH, RYK, DDR, ROS, RET, LTK,  
20 ROR1, or MUSK.
5.    The crystalline polypeptide of Claim 3 in which the  
cytoplasmic tyrosine kinase is SRC, BRK, BTK, CSK, ABL,  
ZAP70, FES, FAK, JAK, or ACK.  
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6.    A derivative crystal comprising the crystalline  
form of the polypeptide of Claim 1, 2, 3, 4 or 5 in a  
covalent association with a heavy metal atom.
- 30        7.    A co-crystal comprising the crystalline form of the  
polypeptide of Claim 1, 2, 3, 4 or 5 in association with a  
compound such as a cofactor, substrate, substrate analog,  
inhibitor, or allosteric effector.
- 35        8.    The co-crystal of Claim 7 in which the compound is  
a non-hydrolyzable analog of ATP.

9. A crystal of an FGF receptor tyrosine kinase domain protein, wherein the crystal is characterized by having monoclinic unit cells and space group symmetry C2.
- 5 10. The crystal of Claim 9, wherein the FGF receptor tyrosine kinase domain protein is FLGK.
11. The FLGK crystal of Claim 10, wherein the monoclinic unit cells have dimensions of about  $a=208.3 \pm 0.2$   
10 Å,  $b=57.8 \pm 0.2$  Å,  $c=65.5 \pm 0.2$  Å and  $\beta=107.2^\circ \pm 0.2^\circ$ .
12. The FLGK crystal of Claim 10, wherein the monoclinic unit cells have dimensions of about  $a=211.6 \pm 0.2$   
15 Å,  $b=51.3 \pm 0.2$  Å,  $c=66.1 \pm 0.2$  Å and  $\beta=107.7^\circ \pm 0.2^\circ$ .
13. The FLGK crystal of Claim 10, wherein the crystal is a native crystal.
14. The native FLGK crystal of Claim 13, wherein the  
20 FLGK has a three-dimensional structure characterized by the atomic structure coordinates of Table 3.
15. The FLGK crystal of Claim 10, wherein the crystal is a heavy atom derivative crystal.
- 25 16. The FLGK crystal of Claim 10, wherein the crystal is a co-crystal.
17. The co-crystal of Claim 16, wherein the FLGK  
30 protein has a three-dimensional structure characterized by the atomic structure coordinates of Table 4.
18. A polypeptide corresponding to the catalytic domain of a non-insulin receptor tyrosine kinase, containing at  
35 least about 20 amino acid residues upstream of the first glycine in the conserved glycine-rich region of the catalytic domain, and at least about 17 amino acid residues downstream

of the conserved arginine located at the C-terminal boundary of the catalytic domain.

19. The polypeptide of Claim 18 in which the non-  
5 insulin receptor tyrosine kinase is a receptor tyrosine kinase.

20. The polypeptide of Claim 18 in which the non-  
insulin receptor tyrosine kinase is a cytoplasmic tyrosine  
10 kinase.

21. The polypeptide of Claim 18 in which the non-  
insulin receptor tyrosine kinase is FGF-R, PDGF-R, KDR, CCK4,  
MET, TRKA, AXL, TIE, EPH, RYK, DDR, ROS, RET, LTK, ROR1, or  
15 MUSK.

22. The polypeptide of Claim 20 in which the  
cytoplasmic kinase is SRC, BRK, BTK, CSK, ABL, ZAP70, FES,  
FAK, JAK, or ACK.  
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23. The polypeptide of Claim 21 or 22 having the amino  
acid sequence shown in FIGS. 6A or 6B.

24. A method of using the polypeptide of Claim 18, 19,  
25 20, 21 or 22 to form a crystal, comprising:

- (a) mixing a volume of polypeptide solution with a reservoir solution; and
- (b) incubating the mixture obtained in step (a) over the reservoir solution in a closed container, under  
30 conditions suitable for crystallization.

25. A method of obtaining FGF receptor tyrosine kinase domain polypeptide in crystalline form, the method comprising the steps of:

- 35 (a) mixing a volume of polypeptide solution with an equal volume of reservoir solution, wherein the polypeptide solution comprises 1 mg/mL to 60 mg/mL FGF-type

tyrosine kinase domain protein, 10 mM to 200 mM buffering agent, 0 mM to 20 mM dithiothreitol and has a pH of about 5.5 to about 7.5, and wherein the reservoir solution comprises 10% to 30% (w/v) polyethylene glycol, 0.1 M to 0.5 M ammonium sulfate, 0% to 20% (w/v) ethylene glycol or glycerol, 10 mM to 200 mM buffering agent and has a pH of about 5.5 to about 7.5; and

(b) incubating the mixture obtained in step (a) over said reservoir solution in a closed container at a temperature between 0° and 25° until crystals form.

26. The method of Claim 25, wherein the polypeptide solution comprises about 10 mg/mL FGF receptor tyrosine kinase domain, about 10 mM sodium chloride, about 2 mM dithiothreitol, about 10 mM Tris-HCl and has a pH of about 8; the reservoir buffer comprises about 16% (w/v) polyethylene glycol (MW 10000), about 0.3 M ammonium sulfate, about 5% ethylene glycol or glycerol, about 100 mM bis-Tris and has a pH of about 6.5; and the temperature is about 4°C.

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27. The method of Claim 25, wherein the polypeptide solution includes a compound such as a cofactor, substrate, substrate analog, inhibitor or allosteric effector.

25 28. The method of Claim 25, wherein the compound is a non-hydrolyzable analog of ATP.

29. A [cDNA] <sup>nucleic acid sequence</sup> encoding an FGF receptor tyrosine kinase domain (protein), wherein a coding strand of the [cDNA] has the nucleotide sequence of SEQ ID NO:5.

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